The specification has been objected to because of the following informalities. First, on page 25, lines 24-29 the structure is surrounded by text. Applicants have amended page 25, lines 25-29, such that the structure is no longer surrounded by text. In addition, on page 22, line 25, the spelling of "moieity" has been corrected to read "moiety". Accordingly, applicants request that the objection be withdrawn.

Second, page 36 of the specification is a blank sheet. Applicants have requested that page 36 be omitted. Accordingly, applicants request that the objection be withdrawn.

Finally, the Office Action states that the continuing data section of the application transmittal form does not claim priority for PCT No. PCT/US96/08659 and suggests that the priority claimed for this application be deleted. According to M.P.E.P. § 201.13 and 37 CFR 1.55:

> The claims to priority need be in no special form and may be made by the attorney or agent if the foreign application is referred to in the oath or declarations as required by § 1.63.

Applicants wish to draw the Examiner's attention to the declaration submitted in response to the Notice to File Missing Parts in which foreign priority benefits under Title35 U.S.C. § 119 were claimed for PCT/US96/08549. Accordingly, applicants request that the objection be withdrawn.

Loss of Priority Date:

The Examiner states that the applicant is not afforded the priority date of the parent application because the species the applicant has elected contains new matter.

The present application is a continuation-in-part of application of Ser. No. 09/134,072, filed August 13, 1998; which is a continuation of Ser. No. 08/971,855, filed November 17, 1997, now abandoned; which is a continuation of provisional Ser. No. 60/063,328, filed October 27, 1997; which is a continuation of Ser. No. 08/486,968, filed June 7, 1995, now U.S. Pat. No. 5,707,605; which is a continuation of Ser. No. 08/460,511,

filed June 2, 1995, now abandoned. Priority is claimed for PCT No. PCT/US96/08549, filed June 3, 1996.

An application is entitled to the benefit of the filing date of a prior non-provisional application if the invention being claim was disclosed in the prior application, there was copendency, a reference was made to the prior application, and the application claiming the benefit of the earlier date was filed by an inventor or inventors named in the prior application. See M.P.E.P. § 201.11.

The invention being claimed in the pending application, is directed towards an MRI agent comprising DOTA, Gd(III) and a peptide blocking moiety comprising a linker. This invention is disclosed in U.S. Patent No. 5,707,605 at column 14, lines 54-65, describing blocking moieties comprising peptides; column 17, lines 12-44, describing attachment of blocking moieties via linker groups. At least one of the inventors, Thomas Meade is named in both applications, a reference to U.S. Patent No. 5,707,605 appears in the specification at page 1, lines 7-8, and copendency is established in the specification at page 1, lines 1-9.

Accordingly, applicants are entitled to the priority date of the parent applications.

New Matter Rejection under 35. U.S.C. § 112, first paragraph:

Claims 12-19 are rejected under 35 U.S.C., first paragraph, as containing new matter.

Applicants elected an MRI contrast agent comprising a chelator (i.e., "substituted DOTA") substituted with a blocking moiety (i.e., a peptide). In the structure claimed, three of the four arms of the chelator, represented by X_1-X_4, are COO^- and one of the four arms is substituted with a peptide blocking moiety. In addition, the peptide blocking moiety is attached via a linker, designated as R_{26}. See Response to Restriction and Preliminary Amendment mailed June 21, 2000.

Support for the species elected by the Applicants is found in the specification. First, support for a "substituted DOTA" agent is found in Structure 2, page 15, lines 8-12. Support for a "substituted DOTA" in which three of the arms are COO- and on of the arms is a blocking moiety is found in Structure 8, page 33, lines 3-14. By making all of the R groups

hydrogen, three of the four arms COO^- and one of the four arms a blocking moiety, the basic structure elected by the applicants is represented by Structure 8.

Support for a peptide blocking moiety, attached via a linker to one of the four arms is found at page 20, lines 7-12:

> By "blocking moiety" or grammatical equivalents herein is meant a functional group associated with the chelator metal ion complexes of the invention which is capable of interacting with a target substance and which is capable, under certain circumstances, of substantially blocking the exchange of water in at least one inner coordination site of the metal ion of the metal ion complex.

and at page 20, lines 17-21:

> A blocking moiety may comprise several components. The blocking moiety has a functional moiety which is capable of interacting with a target substance, as outlined below. This functional moiety may or may not provide the coordination atom(s) of the blocking moiety. In addition, blocking moieties may comprise one or more linker groups to allow for correct spacing and attachment of the components of the blocking moiety.

Support for a linker group selected from $(CH_2)CO^-$, $(CO)CH_2)_n$) is found at page 28, line 18 through page 29, line 18:

> It should be appreciated that the blocking moieties of the present invention may further comprise a linker group as well as a functional blocking moiety. That is, blocking moieties may comprise functional blocking moieties in combination with a linker group and/or a coordination site barrier.
>
> Linker groups (sometimes depicted herein as R_{26}) will be used to optimize the steric considerations of the metal ion complex. That is, in order to optimize the interaction of the blocking moiety with the metal ion, linkers may be introduced to allow the functional blocking moiety to block or occupy the coordination site. In general, the linker group is chosen to allow a degree of structural flexibility. For example, when a blocking moiety interacts with a physiological agent which does not result in the blocking moiety being cleaved from the complex, the linker must allow some movement of the blocking moiety away from the complex, such that the exchange of water at at least one coordination site is increased.
>
> Generally, suitable linker groups include, but are not limited to, alkyl and aryl groups, including substituted alkyl and aryl groups and heteroalkyl

> (particularly oxo groups) and heteroaryl groups, including alkyl amine groups, as defined above. Preferred linker groups include p-aminobenzyl, substituted p-aminobenzyl, diphenyl and substituted diphenyl, alkyl furan such as benzylfuran, carboxy, and straight chain alkyl groups of 1 to 10 carbons in length. Particularly preferred linkers include p-aminobenzyl, methyl, ethyl, propyl, butyl, pentyl, hexyl, acetic acid, propionic acid, aminobutyl, p-alkyl phenols, 4-alkylimidazole. (emphasis added).

> Support for a peptide blocking moiety is found at page 22 lines 25-26:
>
> For example, when the enzyme target substance is a protease, the blocking moiety may be a peptide or polypeptide which is capable of being cleaved by the target protease.

Finally support for proteases being selected from the group consisting of caspase, interleukin 1 beta-converting enzyme, cysteine protease, serine protease, calpain, cathepsin and metalloproteinase is found at page 22, lines 13-21:

> Enzymes such as lactase, maltase, sucrase or invertase, cellulase, α-amylase, aldolases, glycogen phosphorylase, kinases such as hexokinase, proteases such as serine, cysteine, aspartyl and metalloproteases may also be detected, including, but not limited to, trypsin, chymotrypsin, and other therapeutically relevant serine proteases such as tPA and the other proteases of the thrombolytic cascade; cysteine proteases including: the cathepsins, including cathepsin B, L, S, H, J, N and O; and calpain; and caspases, such as caspase-3, -5, -8 and other caspases of the apoptotic pathway, and interleukin-converting enzyme (ICE).

Accordingly, the specification does support an MRI agent comprising a "substituted DOTA chelator comprising a Gd(III) metal ion, and in which one of the four arms is substituted with a peptide blocking moiety attached via a linker." Thus, Claims 12-19 do not contain new matter. Applicants request that the rejection under 35 U.S.C. § 112, first paragraph be withdrawn.

Rejection Under 35 U.S.C. § 103(a):

Claims 1, 6, 7, 12, 16 and 17 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Margerum *et al.* WO 95/28966.

To be considered as a prior art reference under 35 U.S.C. § 103, a reference must constitute prior art under 35 U.S.C. § 102. See M.P.E.P. § 2141.01 (I). To qualify as a prior art reference under 35 U.S.C. § 102 (a) or (b) the date the patent is made available to the public is the date it is available as a 35 U.S.C. § 102(a) or (b) reference. See M.P.E.P. § 2126. To be eligible as prior art under 35 U.S.C. § 102(e), the reference must be a U.S. patent. See M.P.E.P. § 102(e). Therefore, under 35 U.S.C. § 102(a) or (b) Magerum *et al.* is available as a prior art reference on its publication date, November 2, 1995. Magerum *et al.* is not available as a prior art reference under 35 U.S.C. § 102(e).

As stated above, support for the present invention is found in U.S. Patent No. 5,707,605, filed June 7, 1995. Thus, the present application claims priority to the June 7, 1995 filing date. As the filing date of June 7, 1995 precedes the November 2, 1995 publication date of Margerum *et al.*, Magerum *et al.* is not available as a prior art reference under 35 U.S.C. §§ 102(a), (b) or (e). As Magerum *et al.* is not available as a prior art reference under 35 U.S.C. § 102, it is also not available as a prior art reference under 35 U.S.C. § 103. Accordingly, applicants request the rejection of Claims 12, 16, and 17 under 35 U.S.C. § 103(a) be withdrawn.

Statutory Double Patenting Rejection Under 35 U.S.C. § 101:

Claim 1 is rejected under 35 U.S.C. § 101 as claiming the same invention as that of claim 1 of U.S. Patent No. 5,980,862. Claim 1 has been cancelled. Withdrawal of the rejection is requested.

Claims 6 and 7 are rejected under 35 U.S.C. § 101 as claiming the same invention as that of claims 1 and 6 of U.S. Patent No. 5,707,605. Claims 6 and 7 have been cancelled. Withdrawal of the rejection is requested.

Obviousness-Type Double Patenting Rejection:

Claim 6 is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No. 5,980,862. Claim 1 is

rejected under the same doctrine as being unpatentable over claims 1, 6 and 7 of U.S. Patent No. 5,707,605.

Claims 1 and 6 have been cancelled. Applicants request withdrawal of the rejection.

The Commissioner is authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 06-1300 (our Order No. A-58634-6/RFT/RMS/RMK).

Dated: 2/28/01

Respectfully submitted,

FLEHR HOHBACH TEST
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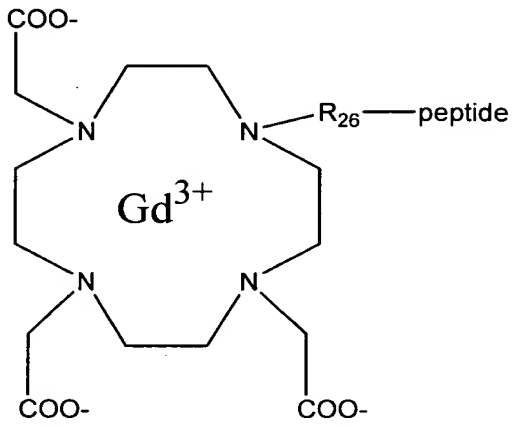
Appendix of Pending Claims

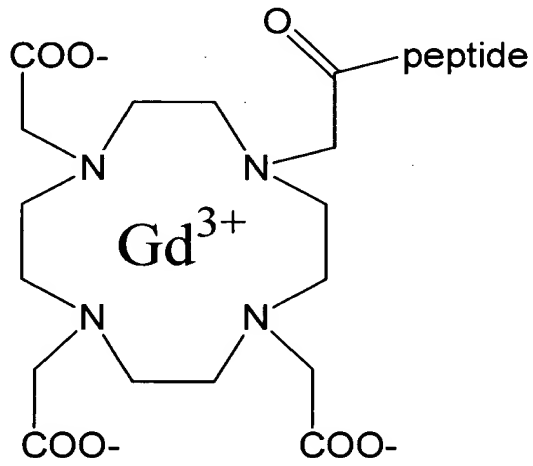
12. An MRI agent according to claim 1 having the formula:



wherein R_{26} is a linker.

16. (Amended) An MRI agent according to claim 12[, 13 or 14] wherein R_{26} comprises -$(CH_2)CO)$-.

17. An MRI agent according to claim 16 having the formula:



--20. An MRI agent according to claim 12 wherein R_{26} comprises -$(CO(CH_2)_n)$-.

21. An MRI agent according to claim 12 wherein R_{26} comprises p-aminobenzyl.

22. An MRI agent according to claim 12 wherein said peptide inhibits a protease.

23. An MRI agent according to claim 22 wherein said protease is selected from the group consisting of caspase, interleukin 1 beta-converting enzyme, cysteine protease, serine protease, calpain, cathepsin and metalloproteinase.--